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EXAMINER	
BERTAGNA, ANGELA MARIE	
ART UNIT	**PAPER NUMBER**
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,831	KARLSEN, FRANK	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,30 and 32-39* is/are pending in the application.

4a) Of the above claim(s) *34-37 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,30,32,33 and 38* is/are rejected.

7)☒ Claim(s) *1-5,30,32,33 and 38* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL REJECTION

Status of the Application

1. Applicant's response filed January 22, 2007 is acknowledged. Claims 1-5, 30, and 32-39 are currently pending. Claims 1-5 have been amended, and claims 6-29 and 31 have been canceled. Claims 32-39 are new.

Election/Restrictions

2. Newly submitted claims 34-37 and 39 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 34-37 and 39 are drawn to a method of detecting HPV mRNA comprising performing a NASBA reaction using a primer pair comprising SEQ ID NO: 16 and SEQ ID NO: 20 and detecting the reaction products using a probe comprising SEQ ID NO: 18. The primers and probes of claims 1-5, 30, 32, 33, and 38 are related to the methods of claims 34-37 and 39 as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, the oligonucleotides of claims 1-5, 30, 32, 33, and 38 can be used in a process materially different from that of claims 34-37 and 39. For example, these oligonucleotides could be used as probes in a Northern or Southern blot.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution

on the merits. Accordingly, claims 34-37 and 39 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Objections

3. Claims 1-5, 30, 32, 33, and 38 are objected to because of the following informalities: The acronym NASBA should be written out at the time of its first appearance in the claims in order to avoid confusion. Appropriate correction is required.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 2, and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable in view of Shimada et al. (EP 0 402 132 A2; cited previously) in view of Buck et al. (Biotechniques 1999; cited previously) and further in view of Simpkins et al. (Letters in Applied Microbiology (2000); cited previously).

Shimada teaches primers and probes for amplification and detection of HPV.

Regarding claims 1, 2, and 4, Shimada teaches an oligonucleotide 20 nucleotides in length that matches exactly the sequence of the instant SEQ ID No: 16 in 18 of 20 nucleotides (see Table 2, sequence p18-3). The only difference between the instant SEQ ID No: 16 and the oligonucleotide of Shimada is the addition of two nucleotides to the 3' end in the instantly claimed oligonucleotide not present in the Shimada oligonucleotide.

Shimada does not teach that the oligonucleotide is modified at the 5' end to contain the T7 promoter sequence GATGCAAGGTCGCATATGAG for use as a NASBA P2 primer.

Buck analyzed the effect of primer design strategy on the performance of DNA sequencing primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer

functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Simpkins teaches a NASBA method for detection of Salmonella enterica.

Regarding claims 1, 2, and 4, Simpkins teaches a NASBA P2 primer containing the sequence GATGCAAGGTCGCATATGAG at the 5' end, where the sequence GATGCAAGGTCGCATATGAG is specific for the Nuclisens™ ruthenium-linked oligonucleotide detection probe (see Primers & probes section, page 76). Simpkins further teaches that NASBA using an mRNA template is a more accurate method of quantifying nucleic acids compared to conventional PCR or RT-PCR (see page 75, col. 1 – page 76, col. 2).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to modify the 3' terminus of the oligonucleotide disclosed by Shimada in order to obtain the instantly claimed oligonucletide of SEQ ID No: 16. As noted above, the differences between the instantly claimed oligonucleotide and the oligonucleotide of Shimada are minor – two additional 3'-terminal nucleotides are present in the instant sequence. Absent any disclosed advantage for using the instantly claimed oligonucleotide, the differences appear to stem from

user preference rather than an improvement over the oligonucletide taught by Shimada. Furthermore, since Buck clearly demonstrated the equivalence of primer sequences, the ordinary biochemist could have anticipated a reasonable level of success in using the modified primers to amplify mRNA transcripts from HPV.

Attention is also directed to the court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995) where the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious.

Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 5 of the reference)."

As noted above, the prior art of Shimada teaches an oligonucleotide highly similar to the instant SEQ ID No: 16, with the only difference relating to the addition of two nucleotides at the 3' terminus of the instant sequence. Furthermore, Shimada taught regions of approximately 100 nucleotides designated as useful for primer design for the detection of HPV (Table 1, Sequence 5 (HPV18 from Region II)). Since the claimed primer simply represents a structural homolog, which was derived from sequences suggested by the prior art of Shimada as useful for primers and probes for the detection of HPV, and in particular for detection of transcripts of the E6 gene, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primer is *prima facie* obvious over the cited references in the absence of secondary considerations.

It also would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to modify the oligonucleotide of Shimada to include the T7 promoter sequence GATGCAAGGTCGCATATGAG to permit its use in the NASBA reaction, because Simpkins taught that inclusion of a generic probe sequence in the NASBA P2 primer was useful for detection of the amplified products using electrochemiluminescence (ECL). Moreover, Simpkins taught that NASBA was more accurate for amplification of RNA than the PCR amplification method taught by Shimada (see page 75, col. 1 – page 76, col. 2). One of ordinary skill would have expected the oligonucleotide of Shimada to work reasonably well in a NASBA reaction, because Shimada demonstrated that the oligonucleotide was capable of amplifying HPV, and incorporation of the generic probe sequence GATGCAAGGTCGCATATGAG could have been accomplished using standard synthesis methods known in the art. Therefore, an ordinary practitioner, interested in a more accurate RNA amplification method for detection of mRNA transcripts from HPV, would have been motivated to modify the oligonucleotide of Shimada for use in a NASBA reaction, specifically by incorporating the generic probe sequence GATGCAAGGTCGCATATGAG, as suggested by Simpkins, in order to detect the NASBA products using ECL, thus resulting in the instantly claimed invention.

6. Claims 1, 5, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable in view of Shimada et al. (EP 0 402 132 A2; cited previously) in view of Tyagi et al. (Nature Biotechnology (1996) 14: 303-308; newly cited) and further in view of in view of Buck et al. (Biotechniques (1999); cited previously).

Shimada teaches primers and probes for amplification and detection of HPV.

Regarding claims 1 and 5, Shimada teaches an oligonucleotide 20 nucleotides in length that matches exactly the instantly claimed SEQ ID No: 18 in 18 out of a possible 20 nucleotides (see Table 3, sequence p818 II). The oligonucleotide of Shimada contains two additional nucleotides at the 5' end (namely, CC) and lacks three nucleotides at the 3' end (namely, ATG) present in the instantly claimed SEQ ID No: 18.

Shimada does not teach that the probe is a molecular beacon probe.

Tyagi taught molecular beacons for rapid, specific detection of amplified nucleic acids. Regarding claims 1 and 30, Tyagi stated, "The probes are particularly suited for monitoring the synthesis of specific nucleic acids in real time. When used in nucleic acid amplification assays, gene detection is homogeneous and sensitive, and can be carried out in a sealed tube (abstract)."

Buck analyzed the effect of primer design strategy on the performance of DNA sequencing primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby

testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to modify the oligonucleotide taught by Shimada in order to obtain the instantly claimed oligonucletide of SEQ ID No: 18. As noted above, the differences between the instantly claimed oligonucleotide and the oligonucleotide of Shimada are minor – the Shimada sequence contains an additional two 3'-terminal nucleotides and lacks the first three 5'-terminal nucleotides of the instant sequence. Absent any disclosed advantage for using the instantly claimed oligonucleotide, the differences appear to stem from user preference rather than an improvement over the oligonucletide taught by Shimada. Furthermore, since Buck clearly demonstrated the equivalence of primer sequences, the ordinary biochemist could have

anticipated a reasonable level of success in using the probes (which unlike primers must only hybridize and not undergo extension) taught by Shimada to detect mRNA transcripts from HPV.

Attention is also directed to the court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995) where the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

> "Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 5 of the reference)."

As noted above, the prior art of Shimada teaches an oligonucleotide highly similar to the instant SEQ ID No: 18, with the only differences relating to 2-3 nucleotides at the termini. Furthermore, Shimada taught regions of approximately 100 nucleotides designated as useful for primer design for the detection of HPV (Table 1, Sequence 5 (HPV18 from Region II)). Since the claimed probe simply represents a structural homolog, which was derived from sequences suggested by the prior art of Shimada as useful for primers and probes for the detection of HPV, and in particular for detection of transcripts of the E6 gene, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed probe is *prima facie* obvious over the cited references in the absence of secondary considerations.

It also would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize a molecular beacon based on the oligonucleotide of Shimada for detection

of amplified products. Tyagi expressly taught that molecular beacons offered highly specific, sensitive, single-tube, real-time detection of amplified products (see above). The ordinary practitioner would have been motivated by the teachings of Tyagi to modify the probe taught by Shimada to function as a molecular beacon in order to achieve the advantages of beacon detection discussed above. Since Tyagi taught that the required fluorophores were attached to the probe during its chemical synthesis, the skilled artisan would have expected a reasonable level of success in adapting the oligonucleotide of Shimada into a molecular beacon.

7. Claims 2 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Von Knebel-Doberitz et al. (USPN 6,027,891; cited previously) in view of Kievits (J. of Virological Methods, 1991; cited previously) and further in view of Yates et al. (J. of Clinical Microbiology, 2001; cited previously).

Von Knebel-Doberitz teaches an oligonucleotide comprising a sequence perfectly complementary to that of the instant SEQ ID NO: 20 (see the Sequence Listing, where SEQ ID Nos: 4 and 22 of Von Knebel-Doberitz are oligonucleotide primers of 21 nucleotides that contain the exact complement of the instant SEQ ID No: 20 with the addition of a single thymine nucleotide at the 5' end).

Von Knebel-Dobertiz does not teach a NASBA P1 primer comprising the instant SEQ ID NO: 20.

Kievits teaches nucleic acid sequence based amplification (NASBA) as a method for detection of HIV-1 in clinical samples (see abstract). In a review of the principles of the method,

Kievits notes the requirement of an RNA polymerase promoter sequence, such as the sequence for the T7 RNA polymerase (AATTCTAATACGACTCACTATAGGG) (see Figures 1 and 2) in order to synthesize the amplified RNA produced by the method.

Yates teaches a method for detecting HBV using NASBA and molecular beacon detection. This method uses a P1 NASBA primer containing the sequence AATTCTAAATACGACTCACTATAGGGAGAAGG at the 5' end to function as a T7 RNA polymerase promoter sequence (see Table 1, page 3657).

It would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to modify the oligonucleotide of Von Knebel-Dobritz et al. to contain a T7 RNA polymerase promoter sequence such as AATTCTAAATACGACTCACTATAGGGAGAAGG for use in a NASBA reaction, because Kievits et al. taught that inclusion of such a promoter sequence is essential for conducting the NASBA reaction (see Figures 1 & 2; page 276). Although Kievits taught the use of a promoter sequence that is 6 nucleotides shorter than the instantly claimed sequence, Yates successfully used a NASBA P1 primer containing the longer, instantly claimed sequence, thereby providing the ordinary artisan with an alternative promoter sequence and a reasonable expectation of success in performing NASBA using such a primer. Moreover, Kievits also taught that NASBA has several advantages over the conventional amplification methods taught by Von Knebel-Dobritz, including being more suitable for amplification of RNA target sequences and lacking the need for thermocycling (page 274). Therefore, one of ordinary skill in the art, interested in

obtaining a better amplification of mRNA transcripts from the E6 gene of HPV would have been motivated to modify the oligonucleotide of Von Knebel-Dobritz et al. for use in a NASBA reaction by including a T7 RNA polymerase promoter sequence as taught by Kievits or Yates, thus resulting in the instantly claimed invention.

8. Claims 1, 5, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cummins et al. (USPN 5,654,416; cited previously) or Hendricks et al. (WO 91/08312; cited previously) in view of Tyagi et al. (Nature Biotechnology (1996) 14: 303-308).

Regarding claims 1 and 5, Cummins teaches an oligonucleotide (SEQ ID No: 36) 28 nucleotides in length that contains the exact sequence of the instant SEQ ID No: 18 with an additional five nucleotides at the 5' end and two additional nucleotides at the 3' end (see sequence listing, column 43).

Regarding claims 1 and 5, Hendricks teaches a 38 bp oligonucleotide probe for detection of HPV that contains the exact complement of the sequence of the instant SEQ ID No. 18 with an additional seventeen nucleotides at the 5' end (Figure 3, probe no. 18-4). As noted above, a teaching in the prior art of the complement is an inherent teaching of the reverse strand sequence.

Neither Cummins nor Hendricks teaches that the probe is a molecular beacon.

Tyagi taught molecular beacons for rapid, specific detection of amplified nucleic acids. Regarding these probes, Tyagi expressly stated, "The probes are particularly suited for monitoring the synthesis of specific nucleic acids in real time. When used in nucleic acid

amplification assays, gene detection is homogeneous and sensitive, and can be carried out in a sealed tube (abstract)."

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize a molecular beacon based on the oligonucleotide of Cummins or Hendricks for detection of amplified products. Tyagi expressly taught that molecular beacons offered highly specific, sensitive, single-tube, real-time detection of amplified products (see above). The ordinary practitioner would have been motivated by the teachings of Tyagi to modify the probe taught by either Cummins or Hendricks to function as a molecular beacon in order to achieve the advantages of beacon detection discussed above. Since Tyagi taught that the required fluorophores were attached to the probe during its chemical synthesis, the skilled artisan would have expected a reasonable level of success in adapting the oligonucleotide of either Cummins or Hendricks into a molecular beacon.

9. Claims 32, 33, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shimada et al. (EP 0 402 132 A2; cited previously) in view of Von Knebel-Doberitz et al. (USPN 6,027,891; cited previously) and further in view of Buck et al. (Biotechniques 1999; cited previously) and further in view of Kievits et al. (Journal of Virological Methods (1991) 35: 273-286; cited previously).

Shimada teaches primers and probes for amplification and detection of HPV (abstract).

Regarding claim 32, Shimada teaches a primer pair for detecting HPV DNA (see Table 2 on page 7). One of the oligonucleotides in this primer pair is an oligonucleotide 20 nucleotides

in length that matches exactly the sequence of the instant SEQ ID No: 16 in 18 of 20 nucleotides (see Table 2, sequence p18-3). This oligonucleotide is a NASBA P2 primer as evidenced by the instant application specification at pages 9-10. The only difference between the instant SEQ ID No: 16 and the oligonucleotide of Shimada is the addition of two nucleotides to the 3' end in the instantly claimed oligonucleotide not present in the Shimada oligonucleotide.

Regarding claim 33, Shimada teaches a primer/probe set comprising a primer pair (see Table 2) and also at least one synthetic or isolated oligonucleotide probe specific for amplification products generated using the primer pair (see Table 3 on page 8 and pages 7-8).

Regarding claim 38, Shimada teaches a reagent kit for detection of HPV comprising a primer pair (page 8, lines 42-50).

As noted above, the primer taught by Shimada does not include the last two 3'nucleotides contained in the instant SEQ ID NO: 16. Also, Shimada does not teach that the second primer in the primer pair is an oligonucleotide comprising SEQ ID NO: 20.

Von Knebel-Doberitz teaches an RT-PCR method for detecting HPV (see abstract).

Regarding claim 32, Von Knebel-Doberitz teaches an oligonucleotide primer that comprises a sequence perfectly complementary to that of the instant SEQ ID NO: 20 (see the Sequence Listing, where SEQ ID Nos: 4 and 22 of Von Knebel-Doberitz are oligonucleotide primers of 21 nucleotides that contain the exact complement of the instant SEQ ID No: 20 with the addition of a single thymine nucleotide at the 5' end).

Regarding claim 33, Von Knebel-Doberitz teaches a primer/probe set comprising a primer pair (see, for example, column 2, lines 59-64) and also at least one synthetic or isolated oligonucleotide probe specific for amplification products generated using the primer pair (column 5, lines 39-41).

Von Knebel-Dobertiz does not teach a NASBA P1 primer comprising the instant SEQ ID NO: 20 or its complementary sequence.

Kievits teaches nucleic acid sequence based amplification (NASBA) as a method for detection of HIV-1 in clinical samples (see abstract). In a review of the principles of the method, Kievits notes the requirement of an RNA polymerase promoter sequence, such as the sequence for the T7 RNA polymerase (AATTCTAATACGACTCACTATAGGG) (see Figures 1 and 2) in order to synthesize the amplified RNA produced by the method. Kievits teaches that NASBA eliminates the need for a complicated and time-consuming reverse transcription step when amplifying an RNA target sequence (page 283).

Yates teaches a method for detecting HBV using NASBA and molecular beacon detection. This method uses a P1 NASBA primer containing the sequence AATTCTAAATACGACTCACTATAGGGAGAAGG at the 5' end to function as a T7 RNA polymerase promoter sequence (see Table 1, page 3657).

Buck analyzed the effect of primer design strategy on the performance of DNA sequencing primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to combine the teachings of Shimada, Von Knebel-Doberitz, Kievits, Yates, and Buck. As discussed in greater detail above (see section 5), the combined teachings of Shimada and Buck result in a NASBA P2 primer comprising SEQ ID NO: 16. Also, as discussed in section 7 above, the combined teachings of Von Knebel-Doberitz, Kievits, Yates, and Buck result in a NASBA P1 primer comprising SEQ ID NO: 20. An ordinary practitioner would also have been

motivated by the teachings of the above references to combine any known primers and probes for amplification and detection of HPV into a primer-probe set. As noted in MPEP 2144.06, combining art-recognized equivalents for the same purpose is prima facie obvious. In the instant case, the prior art suggests that amplification primers comprising SEQ ID NO: 16 and SEQ ID NO: 20 are useful for amplification and detection of the E6 gene of HPV. An ordinary practitioner would have been motivated by these teachings to combine the primers in a primer set for amplification and detection of HPV. Therefore, the primer/probe set and kit of claims 32, 33, and 38 is prima facie obvious in view of the combined teachings of Shimada, Von Knebel-Doberitz, Kievits, Yates, and Buck.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1-5, 30, 32, and 33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10 and 12 of copending Application No. 10/500,832. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '832 application recites the instantly claimed SEQ ID Nos: 16, 18, and 20 (see claim 12 of the '832 application, sequences 4-6 in the claim). Claim 12 of the '832 application further teaches modification of SEQ ID NO: 16 and 20 with the claimed promoter sequences (see fourth and fifth sequences in claim 12). Finally, Claim 10 of the '832 application teaches that the probes are molecular beacons. Therefore, claims 10 and 12 of the '832 application anticipate the instant claims 1-5, 30, 32, and 33.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

12. Claim Objections

Applicant's arguments, see page 6, filed January 22, 2007, with respect to the objection to claims 1-5 and 30 have been fully considered and are persuasive. Applicant's amendment overcomes the objection, and therefore it has been withdrawn.

Rejections under 35 U.S.C. 102

Applicant's arguments, see pages 7-8, filed January 22, 2007, with respect to the rejection of claim 1 under 102(b) as anticipated by Von Knebel-Doberitz and the rejection of claim 1 under 102(e) as anticipated by Anthony have been fully considered and are persuasive.

Neither reference teaches that the nucleic acid comprising SEQ ID NO: 20 (or its complement) additionally comprises a promoter region as required by a NASBA primer. Since the references do not teach all of the elements of claim 1 as amended, the rejections have been withdrawn.

Rejections under 35 U.S.C. 103

A. Shimada, Buck, Simpkins

Applicant's arguments filed January 22, 2007 have been fully considered but they are not persuasive. Applicant argues that the combination of Shimada, Buck, and Simpkins does not render the oligonucleotides of claims 1, 2, and 4 obvious (see pages 8-9 of the response).

Applicant argues that there is no teaching or suggestion in Shimada to modify the disclosed oligonucleotide by the addition of two 3'-terminal nucleotides to result in the instant SEQ ID NO: 16. Applicant also argues that the references do not provide motivation for one of ordinary skill in the art to further modify the sequence taught by Shimada to function as a NASBA P2 primer, since NASBA requires an RNA template and the method of Shimada utilized a DNA template. Finally, Applicant argues that Buck is directed to sequencing primer functionality, and therefore, is not relevant to the instant case (see pages 8-9).

Applicant's arguments were carefully considered but were not found persuasive. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5

USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, the motivation to modify the 3' terminus of the primer sequence taught by Shimada is found on pages 6-7 of the reference. In Table 2 on page 7, Shimada teaches a primer sequence differing from SEQ ID NO: 16 only by the absence of two 3'-terminal nucleotides. In Table 1 on page 6, Shimada teaches regions of the HPV E6 gene to be targeted by the amplification primers presented in Table 2. Region I of HPV-18 displays the primer shown in Table 2 of Shimada flanked by approximately 60 nucleotides on either side. Region I contains the full sequence of the instant SEQ ID NO: 16. This depiction of an HPV-18 region suitable for amplification in combination with the statement by Shimada that a suitable primer contains about 20 nucleotides that hybridize to the above region (page 6, lines 43-49) would have provided motivation for an ordinary practitioner to design a primer comprising any 20 consecutive nucleotides shown in Region I. Further motivation to modify the primer taught by Shimada is provided by In re Deuel, as discussed above. Finally, the instant case does not constitute an "obvious to try" situation. As discussed in MPEP 2145 X B and In re O'Farrell (853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)), an improper "obvious to try" situation results from two kinds of error: (1) the requirement to vary all parameters or try numerous possibilities until arriving at a successful result, where the prior art provides no indication of the critical parameters or which possibilities to try, and (2) the requirement for exploration of a new technology with only general guidance provided by the prior art. In re O'Farrell the court held that the claimed method was obvious since the prior art provided a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the

modification would be successful. In the instant case, the cited references (Shimada, Simpkins, Buck) provide these necessary elements. Shimada taught a 200 nucleotide region of the HPV-18 E6 gene useful for the design of amplification primers and further taught a specific primer targeting this region. Simpkins taught a detailed description of NASBA primer design and further provided motivation for substituting NASBA detection for PCR detection. Finally, the teachings of Shimada, Simpkins, and Buck provide a reasonable expectation of success.

Regarding the modification of SEQ ID NO: 16 for use as a NASBA P2 primer, motivation is found in the express teachings of Simpkins. As noted above, Simpkins taught that NASBA using an RNA template was a more accurate quantification method than conventional PCR using a DNA template (see page 75, col. 1 – page 76, col. 2). An ordinary practitioner of the HPV amplification method taught by Shimada would have been motivated by these teachings of Simpkins to utilize an RNA rather than a DNA template in order to obtain this improved accuracy in the results, and therefore, would have been motivated to modify the primer by addition of the 5' sequence taught by Simpkins in order to amplify and detect HPV using NASBA rather than conventional PCR.

Regarding the relevance of the Buck reference, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Buck is reasonably pertinent to the particular problem with which applicant is concerned. More specifically, Buck teaches that minor modification in primer sequences did not affect their ability to extend on a template. An ordinary practitioner would

have recognized that these teachings of Buck were not limited to the specific case of DNA sequencing primers, but were applicable to primers in general. Therefore, the teachings of Buck are relevant to the NASBA primers of the instant application.

Finally, regarding Applicant's argument that one of ordinary skill would not have had a reasonable expectation of success in obtaining the claimed primer, as noted in MPEP 2143.02, a reasonable expectation of success does not require absolute predictability. As discussed above, the teachings of Shimada that a highly similar primer could function in a PCR method would have provided an ordinary practitioner with a reasonable expectation that a primer containing two additional 3' nucleotides would also be capable of functioning as an amplification primer, especially in light of the teachings of Buck that minor modifications to a primer did not appreciably inhibit extension capability. Therefore, in the absence of evidence of secondary considerations, an ordinary practitioner would have had a reasonable expectation of success in obtaining the claimed primer.

Since none of the above arguments were found persuasive, the rejection of claims 1, 2, and 4, under 103(a) over Shimada in view of Buck and further in view of Simpkins has been maintained.

B. Shimada, Tyagi, Buck

Applicant's arguments (see page 10) filed January 22, 2007 have been fully considered but they are not persuasive.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on

obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

At the outset, it is noted that Applicant's remarks concerning motivation for modifying the 5' terminus of the probe taught by Shimada are not relevant, because the instant claims recite the open language "comprising". Therefore, inclusion of additional nucleotides at the 5' terminus of the probe taught by Shimada is not prohibited by the claim language, and the only relevant difference between the probes is at the 3' terminus, where three nucleotides are absent from the probe taught by Shimada. The motivation to add these three nucleotides to the probe taught by Shimada is found on pages 3, 7, and 8 of the reference. In Table 3 on page 8, Shimada teaches a probe sequence comprising SEQ ID NO: 18 except for the last three 3'-terminal nucleotides. Shimada further teaches that this probe targets "Region II" of the HPV-18 E6 gene in this table. In Figure 2 on page 3, Shimada teaches regions of the HPV E6 gene to be targeted

by the probes presented in Table 3. Region II of HPV-18 shows the probe shown in Table 3 of Shimada flanked by approximately 45 nucleotides upstream and 15 nucleotides downstream. This approximately 100 nucleotide sequence contains the full sequence of the instant SEQ ID NO: 18. This depiction of an HPV-18 region suitable for probe desgin in combination with the statement by Shimada that a suitable probe hybridizes to the above region (pages 7 and 8) would have provided motivation for an ordinary practitioner to design a probe comprising any 20 consecutive nucleotides shown in Region II. Further motivation to modify the 3' terminus of the probe taught by Shimada is provided by In re Deuel, as discussed above. Finally, the instant case does not constitute an "obvious to try" situation. As discussed in MPEP 2145 X B and In re O'Farrell (853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)), an improper "obvious to try" situation results from two kinds of error: (1) the requirement to vary all parameters or try numerous possibilities until arriving at a successful result, where the prior art provides no indication of the critical parameters or which possibilities to try, and (2) the requirement for exploration of a new technology with only general guidance provided by the prior art. In re O'Farrell the court held that the claimed method was obvious since the prior art provided a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful. In the instant case, the cited references (Shimada, Tyagi, Buck) provide these necessary elements. Shimada taught an approximately 100 nucleotide region of the HPV-18 E6 gene ("Region II") useful for the design of hybridization probes and further taught a specific probe targeting this region that is highly similar to the instantly claimed probe. Tyagi provided additional motivation to label the probe with a fluorophore and quencher moiety to create a molecular beacon probe, as discussed above.

Finally, the teachings of Shimada provide a reasonable expectation of success in obtaining a functional hybridization probe designed from the Region II sequence.

Regarding the relevance of the Buck reference, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Buck is reasonably pertinent to the particular problem with which applicant is concerned. More specifically, Buck teaches that minor modification in primer sequences did not affect their ability to extend on a template. An ordinary practitioner would have recognized that these teachings of Buck were not limited to the specific case of DNA sequencing primers, but were applicable to primers and probes in general. An ordinary practitioner would have recognized that if a given primer was capable of extension, it must be capable of hybridization. Therefore, the teachings of Buck are relevant to the probes of the instant application.

Finally, regarding Applicant's argument that one of ordinary skill would not have had a reasonable expectation of success in obtaining the claimed probe, as noted in MPEP 2143.02, a reasonable expectation of success does not require absolute predictability. As discussed above, the teachings of Shimada that a highly similar probe could specifically detect amplified HPV-18 E6 nucleic acids would have provided an ordinary practitioner with a reasonable expectation that the same probe containing three additional 3' nucleotides would also function as a detection probe. Therefore, in the absence of evidence of secondary considerations, an ordinary practitioner would have had a reasonable expectation of success in obtaining the claimed probe.

Since none of the above arguments were found persuasive, the rejection of claims 1, 5, and 30, under 103(a) over Shimada in view of Tyagi and further in view of Buck has been maintained.

C. Von Knebel-Dobertiz, Kievits, Yates

Applicant's arguments filed January 22, 2007 have been fully considered but they are not persuasive. Applicant argues that Von Knebel-Dobertiz teaches the complement of SEQ ID NO: 20, and therefore, fails to provide sufficient motivation to design SEQ ID NO: 20 (page 11). Applicant also argues that a primer comprising SEQ ID NO: 20 and a promoter would not function in the method taught by Von Knebel-Doberitz (page 11).

In response to the first argument, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the teaching of Von Knebel-Doberitz of an oligonucleotide primer useful for amplifying the E6 gene comprising a sequence complementary to the instant SEQ ID NO: 20 would have suggested to one of ordinary skill in the art that the region of the E6 gene to which this primer hybridizes was a useful target for amplification primers. Based on the teachings of Von Knebel-Doberitz, an ordinary practitioner would have been motivated to design either the primer disclosed by Von Knebel-Doberitz or its complement for amplification of E6. An ordinary practitioner would have at once envisioned the nucleic acid

sequence of a primer complementary to the primer disclosed by Von Knebel-Doberitz. An ordinary practitioner would also have recognized that primers are directional molecules, and therefore, would have been motivated to design primers targeting either strand of the E6 gene, depending on the goal of the method. Thus, the teachings of Von Knebel-Doberitz provide motivation for the design of a primer comprising the instant SEQ ID NO: 20.

Regarding the second argument, the suitability of the primers for use in the method taught by Von Knebel-Doberitz is not relevant to the instant claims which are directed to an oligonucleotide primer. As discussed above, the teachings of Von Knebel-Dobertiz provide motivation for an ordinary practitioner to design an oligonucleotide primer based on SEQ ID NO: 20 or its complement. The teachings of Kievits and Yates that NASBA is a superior amplification method provide motivation to further include a promoter region in the primer in order to conduct NASBA.

D. Cummins or Hendricks and Tyagi

Applicant's arguments filed January 22, 2007 have been fully considered but they are not persuasive.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5

USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, as discussed above, Cummins teaches a number of oligonucleotide primers and probes for amplification and detection of HPV (see column 8, line 36 – column 9, line 5 and column 10, lines 44-57). Cummins further teaches that a probe "is an oligonucleotide which is substantially complementary to a nucleic acid sequence of the target nucleic acid…and which is used for detection or capture of the amplified target nucleic acid (column 9, lines 57-61)." An ordinary practitioner would have recognized that the primers (such as SEQ ID NO: 36) taught by Cummins were also capable of functioning as probes, and therefore would have been motivated to design a molecular beacon probe using this oligonucleotide in view of the teachings of Tyagi. Therefore, since a primer of Cummins is also a probe, the construction of a molecular beacon as suggested by Tyagi would not render the nucleic acid inoperable for its intended purpose, but rather, would enhace its ability to function as a probe, since Tyagi taught that molecular beacon probes facilitated homogeneous, sensitive, real-time detection of amplified nucleic acids.

Regarding Hendricks, as discussed above, the teaching of a sequence complementary to the instant SEQ ID NO: 18 provides a clear suggestion of both the disclosed nucleotide sequence and also its complement. In other words, an ordinary practitioner could at once envision the complementary sequence upon seeing the probe taught by Hendricks. An ordinary practitioner would also have recognized that when detecting the double-stranded product of a nucleic acid amplification reaction, either strand could be targeted for hybridization with a detection probe. Since Hendricks taught that a sequence comprising the instant SEQ ID NO: 18 was useful for

detection of HPV (see above), an ordinary practitioner would have recognized that this sequence and its complement were useful for detection probes. This rejection has been maintained.

Obviousness-type Double Patenting Rejection

Applicant's arguments filed January 22, 2007 have been fully considered but they are not persuasive. Applicant argues that since the rejection is provisional, it is premature and should be withdrawn (page 14). MPEP 804 states, "The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in at least one of the applications." Since the conflicting claims remain in the two applications and the provisional rejection is not the only remaining rejection in the instant application, the rejection has been maintained.

Conclusion

No claims are currently allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is 571-272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Angela Bertagna
Examiner, Art Unit 1637
March 29, 2007

amb

JEFFREY FREDMAN
PRIMARY EXAMINER
3/30/07